REMARKS

In the Office Action dated March 9, 2000, claims 1-20 are pending, claims 4-20 are withdrawn from consideration, and claims 1-3 are rejected. Non-elected claims 4-20 will be cancelled at an appropriate time for filing a divisional application.

Reference is made to the accompanying Declaration under 37 CFR §1.132 by James Clagett which is being submitted along with this amendment.

Claims 1-2 are rejected under 35 U.S.C. 103(a), as being unpatentable over Gleisner (*Inflammation* 1981) in view of Oxford dictionary of Biochemistry and Molecular Biology (1981) and Casale and Dumitrascu, and further in view of Kermode (*Biochem. J.*, 1991, reference AD), Ferry (*Gastroenterology*, 1989) and Anderson (*Digest. Dis. Sci.*, 1992).

Gleisner was relied upon for teaching that formyl Met peptides are capable of reducing the effects of other proinflammatory agents in that they inhibit the evoked mast cell degranulation and histamine release. The Oxford Dictionary of Biochemistry and Molecular Biology was relied upon for teaching that antihistamine drugs are used in the treatment of allergy reactions. Casale and Dumitrascu were relied upon for teaching that mast cells are the most important cells in the development of an allergenic response. Kermode, Ferry and Anderson were relied upon for teaching that formyl Met peptides such as f-Met-Leu-Phe, F-Met-Leu-Phe-Phe and F-Nle-Leu-Phe-Tyr are functional equivalents.

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The rejection is respectfully traversed.

The present invention is drawn to a method for treating an allergy reaction by administering a peptide having the formula f-Met-Leu-X where X is selected from the group consisting of Tyr, Tyr-Phe, Phe-Phe and Phe-Tyr.

Gleisner suggests that f-Met-Leu-Phe may have an inhibiting effect on mast cell degranulation but fails to show any inhibiting effect for other formyl peptides. For example, Table 1 on page 15, shows that the closely related peptides f-Met-Phe and Met-Phe had little inhibitory effect on mast cell degranulation. It is **not** obvious from Gleisner that structurally similar compounds will have the same effect or the same potency. Furthermore, Gleisner did **not** test any of the peptides of the presently claimed invention. Later references, such as Kermode, Ferry and Anderson, which do address the claimed peptides, teach that these peptides have pro-inflammatory activity and thus would stimulate, not treat, an allergic reaction.

The Oxford dictionary of Biochemistry and Molecular Biology (1981) teaches that antihistamines are used to treat allergic reactions. However, there is no teaching or suggestion that formyl Met peptides can act as antihistamines.

Gleisner and Dumitrascu teach that mast cells are important in the development of allergenic response. However, there is no teaching or suggestion that

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formyl Met peptides would be useful for treating an allergic reaction.

Kermode, Ferry and Anderson were relied upon for teaching that formyl Met peptides such as f-Met-Leu-Phe, F-Met-Leu-Phe-Phe and F-Nle-Leu-Phe-Tyr are functional equivalents.

In fact, Kermode, Ferry and Anderson teach that different formyl Met peptides are **not** functional equivalents.

Kermode establishes that different fMLP peptides have widely differing affinities for the fMLP peptide receptor (page 718, left column, lines 5-9).

> The equilibrium dissociation constant (K_d) for high-affinity binding had a range of **1300-fold** between the least potent (fVal-Leu-Phe) and the most potent (fMet-Leu-Phe-Phe) of the seven formyl peptide analogues, whereas the K_d for the low-affinity binding varied **9700-fold** (Table 1).***[emphasis added]

Furthermore, Kermode states that the strength of the binding of the fMLP peptide to the receptor correlated to the biological potency of the peptide (abstract, page 715, lines 5-6):

> ***The relative potencies of the formyl peptide analogues for stimulation of degranulation correlated will with their relative potencies for high-affinity, but not low-affinity, [receptor] binding.***

Thus, Kermode teaches that the different fMLP peptides have a wide range of affinities for the receptor and that this in turn means their biological potencies vary widely. In other words, Kermode teaches that the different formyl Met peptides are

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not functionally equivalent.

Similarly, Ferry teaches that different formyl Met peptides are **not** functionally equivalent (page 65, left column middle paragraph):

> Formyl-methionyl-leucyl-tyrosine, rather than the naturally occurring f-met-leu-phe was used in these studies to permit ^{125}I labeling. This peptide is bio-active but **substantially less potent** in inducing inflammation than f-met-leu-phe.***[emphasis added]

Anderson is directed to the study of the structural requirements of N-formyl peptides for **hepatobiliary secretion** (see page 248, Abstract, lines 3-6).

> ***To determine the molecular structural requirements for hepatobiliary excretion of formyl-methionyl peptides, structure-activity studies using portal venous infusions of 24 structural analogs of formyl-met-leu-tyr were performed in rats with biliary cannulae.***

Anderson further teaches that there is no basis for correlating the ability of the liver to excrete N-formyl peptides with the bioactivity (i.e. mast cell degranulation and chemotaxis) of the N-formyl peptides themselves. At page 254, left column, 4th full paragraph:

> Our studies, while confirming the importance of N-acylation of peptides in hepatic extraction and excretion, **do not** elucidate the mechanism of uptake and transport.***[emphasis added]

And, at page 254, right column, last paragraph:

> ***[S]ince both trace [quantity] and mass [quantity] infusions of peptides were equally excreted into the bile, the efficiency of secretion **did not correlate** with bioactivity (e.g. FMLT vs nonbioactive FMLT sulfoxide) and excretion of peptide was complete within several minutes, too short a time scale for leukocyte recruitment.

Thus, Anderson teaches the "requirements for the core structure of biologically

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active formyl Met peptide analogs", wherein the **biological activity**, to which reference is made, **is the ability of the peptides to be excreted by the liver**. Anderson teaches nothing about the requirements for the core structure of biologically active peptide analogs wherein the biological activity, to which reference is made, is related to allergy or inflammation (i.e. mast cell degranulation and chemotaxis). In fact, Anderson teaches that the mechanism by which N-formyl peptides are excreted by the liver is unknown and may be totally separate from the mechanism by which they are involved in the inflammatory response. Thus, Anderson does **not** teach that different formyl Met peptides are functionally equivalent.

Therefore, Gleisner teaches that a non-claimed peptide, f-Met-Leu-Phe has inhibitory activity toward mast cell degranulation. Gleisner does not address any of the peptides of the claimed invention. Gleisner also teaches that similar formyl Met peptides are **not** functionally equivalent. The supporting references, Kermode, Ferry and Anderson, also teach that different formyl Met peptides are **not** functionally equivalent. Furthermore, the only references which do address peptides of the claimed invention teach that those peptides have pro-inflammatory or allergy stimulating effects.

Therefore, based on the prior art of record, it not seen how it would have been obvious for one of ordinary skill in the art to reasonably predict the results for treating an allergy reaction using the peptides of the present invention. Furthermore, the

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surprisingly remarkable inhibitory activities of the peptides of the present invention would not have been obvious to one of ordinary skill in the art from the prior art teachings.

Only present Applicant has discovered the usefulness of administering the peptides of the claimed invention as a method for treating an allergy reaction. Applicants demonstrated in the specification that many formyl peptides have no effect on inhibition of mast cell degranulation. Table 1 (page 20) shows the results of an experiment wherein compound 48/80 was injected into rat skin to induce mast cell degranulation and the amount of inhibition of degranulation for a variety of formyl Met peptides was quantitated. fMLP has an effect of only 30% inhibition of mast cell degranulation in the *in vitro* test of the instant application. Surprisingly and unexpectedly, the compounds of the present invention have an effect of 55% or more inhibition of mast cell degranulation with the preferred f-Met-Leu-Phe-Phe providing 100% inhibition of mast cell degranulation in the *in vitro* test.

Applicants have tested the effects on inflammation (i.e. allergic response) induced by prior art peptides, namely fMLP discussed in Gleisner and other references, as compared to peptides of the present invention, namely fMLPP. The results of these experiments are presented in the accompanying Declaration of Dr. Clagett. Briefly, Applicants compared the effects of injecting fMLP or fMLP + fMLPP into the dorsum of mice feet and observed the effects on the injected tissue over time. Applicants found that injection of fMLP alone caused a strong inflammatory effect

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including massive cellular infiltration to the site of injection whereas simultaneous injection with fMLPP blocked this inflammatory response. See the Declaration of James Clagett, paragraphs 10-12.

In short, fMLP exhibited a **pro**-inflammatory or allergy stimulating activity in accord with the teachings of the prior art. However, surprisingly and unexpectedly (in view of the prior art) fMLPP of the present invention exhibited an **anti**-inflammatory activity that blocked the pro-inflammatory response induced by fMLP. See the Declaration of James Clagett, paragraphs 13-16.

In view of the above, it is not seen how the present invention would have been obvious to one of ordinary skill in the art. Reconsideration and withdrawal of the rejections are requested.

Claim 3 is rejected under 35 U.S.C. 103(a) for the reasons set forth with respect to claims 1 and 2, and further in view of Goodman and Gilman ("AL"). The rejection is respectfully traversed.

As discussed above, Gleisner teaches that a non-claimed peptide, f-Met-Leu-Phe has inhibitory activity toward mast cell degranulation. Gleisner does not address any of the peptides of the claimed invention. Gleisner also teaches that similar formyl Met peptides are **not** functionally equivalent.

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The supporting references, Kermode, Ferry and Anderson, also teach that different formyl Met peptides are **not** functionally equivalent.

Furthermore, the references (Kermode, Ferry and Anderson) which do address peptides of the claimed invention teach that those peptides have pro-inflammatory or allergy stimulating effects.

Goodman and Gilman do not teach or suggest the use of the presently claimed f-Met-Leu peptides to treat allergy.

Therefore, based on the prior art of record, it would not have been obvious for one of ordinary skill in the art to develop a method for treating an allergy reaction using the peptides of the present invention. Furthermore, the surprisingly remarkable inhibitory activities of the peptides of the present invention would not have been obvious to one of ordinary skill in the art from the prior art teachings. See the Declaration of James Clagett, paragraphs 7-16.

Thus, it is not seen how the presently claimed invention would have been obvious to one of ordinary skill in the art from any combination of the cited prior art. Reconsideration and withdrawal of the rejections are respectfully requested.

Claims 1-3 were rejected under 35 U.S.C. §112, first paragraph, because it is

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alleged that the claims do not reasonably provide enablement for pharmaceutical use of f-met peptides in the absence of exposure to such pro-inflammatory agents.

Applicants respectfully traverse the rejection.

It is necessary to induce an allergenic response in order to test a compound for its effect on treating the allergenic response. Pre-administration of pro-inflammatory agents was used as a way to generate an experimental model of an allergy reaction. The present invention is directed to a method for treating an allergy reaction. In other words, the method is directed to treating a mammal which has been exposed to an allergy stimulating agent. Therefore, rejection of the claims for lack of enablement for a pharmaceutical use of formyl Met peptides in the absence of exposure to a pro-inflammatory agent is not relevant because exposure to such an agent is a pre-requisite for an allergy reaction and the treatment effect of the present invention. See the Declaration of James Clagett, paragraph 18.

Additionally, Applicants provide considerable discussion for treating allergy reaction using formyl Met peptides, including dosage. Further, an extensive experimental section presents detailed descriptions and results of *in vitro* and *in vivo* experiments showing the administration of formyl Met peptides of the invention can inhibit mast cell degranulation, eosinophil infiltration and mucus accumulation. Data is presented from a Rat skin model for inhibition of mast cell degranulation (pages 17-21), a mouse model of asthma (pages 21-40) and a mouse model of arthritis

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(pages 40-44). Furthermore, the dosages used for treatment of the mouse model of asthma (for example, at page 31, lines 10-14, 5-10 μg/kg of HK-X was administered) and the mouse model of arthritis (for example, at page 43, lines 15-30, 0.4 mg/kg or 4 mg/kg of HK-X was administered) were disclosed and the dosages are within the effective range indicated in the specification at page 12. See the Declaration of James Clagett, paragraphs 19-20.

Furthermore, performing a dose response curve for determination of an optimal dosage would hardly require undue experimentation for one skilled in the art. Indeed, routine experimentation is normal for establishing doses for therapeutic treatments. See the Declaration of James Clagett, paragraph 20.

Applicants submit that it is routine experimentation in the art to determine the useful dose for any particular application and to determine whether a dose has any harmful effects. Applicants have found mast cell degranulation inhibitory effects at very low doses and surprisingly have not found any harmful effects even at high dosages in animal testing to date.

It is respectfully submitted that the description and working examples in the specification provide adequate guidance for one skilled in the art to make and use the claimed invention. In light thereof, reconsideration and withdrawal of the §112 rejections are respectfully requested. If the examiner intends to maintain this rejection, it is requested that specific reasons be set forth regarding why the

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specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims so that applicant can specifically address each such reason.

In view of the amendment and discussion above, and the Declaration of Dr. Clagett, it is respectfully submitted that the present application is in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

Respectfully submitted,

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